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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/032,281	12/21/2001	John Wyrick	WTHD-007CIP	4057
71598 7590 01/14/2008 BOZICEVIC, FIELD & FRANCIS LLP (WHITEHEAD INSTITUTE OF BIOMEDICAL RESEARCH) 1900 UNIVERSITY AVENUE EAST PALO ALTO, CA 94303			EXAMINER HORLICK, KENNETH R	
			ART UNIT 1637	PAPER NUMBER
			MAIL DATE 01/14/2008	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/032,281	<b>Applicant(s)</b> WYRICK ET AL.	
	<b>Examiner</b> Kenneth R. Horlick	<b>Art Unit</b> 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 31 October 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-6, 8, 15-17, 87, 88 and 90-92 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6, 8, 15-17, 87, 88, and 90-92 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

1. It is noted that this application is now being handled by a different examiner, as indicated at the end of this Office action.

2. Upon consideration of the Appeal Brief filed 10/31/07 and new prior art, the finality of the Office action mailed 06/08/07 is hereby WITHDRAWN, and the following new ground of rejection is made.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 8, 15-17, 87, 88 and 90-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Strutt et al. (EMBO J. (1997) 16(12):3621-3631), in view of either of Page et al. (US 5,871,920) or Guilfoyle et al. (US 5,376,549), and further in view of Schena (Tibtech (1998) 16:301-306).

Strutt teaches a method of claim 1 for *identifying a region of a genome of a cell to which a protein of interest binds* (see abstract) comprising the steps of:

*a) crosslinking DNA binding proteins in the cell to genomic DNA of the cell, thereby producing DNA binding protein crosslinked to genomic DNA (see page 3622, column 1 and page 3630, column 2, subheading "In vivo formaldehyde crosslinking of Schneider cells and immunoprecipitation of cross linked chromatin"),*

*b) generating DNA fragments of the genomic DNA crosslinked to DNA binding protein in a), by sonication, thereby producing a mixture comprising DNA fragments to which DNA binding protein is bound (see page 3622, column 2 and page 3630, column 2, subheading "In vivo formaldehyde crosslinking of Schneider cells and immunoprecipitation of cross linked chromatin", where it is indicated that the DNA was sonicated),*

*c) removing a DNA fragment to which the protein of interest is bound from a first portion the mixture produced in b) (see page 3622, column 1 and page 3630, column 2, subheading "In vivo formaldehyde crosslinking of Schneider cells and immunoprecipitation of cross linked chromatin", where antibodies were used to remove the DNA fragment),*

*d) separating the DNA fragment identified in c) from the protein of interest (see page 3622, column 1 and page 3631, column 1, under subheading "In vivo formaldehyde crosslinking of Schneider cells and immunoprecipitation of cross linked chromatin"),*

*e) labeling the DNA fragment of d) with a first label by:*

*i. ligating adaptors to said fragment;*

*iii. amplifying said DNA fragment using a primer that binds to said adaptors; and*

*iv. labeling said DNA fragment either during or after said amplifying to produce a labeled DNA fragment (see page 3622, where Strutt teaches that the sonicated DNA had blunt ends and that blunt end linkers were ligated to the blunt ends, followed by amplification using the primers and see page 3631, column 2, where amplified DNA was labeled radioactively (see page 3623, figure 1)),*

*f) labeling a second portion of the mixture produced in b) with a label to produce a second sample (see page 3622, column 2, where Strutt expressly teaches the use of control immunoprecipitations from the sample of b) as well as figure 1, which shows a control immunoprecipitation compared to the specific PC and GAGA immunoprecipitations).*

*g) combining the labeled DNA fragment of e) and the second sample of f) with a DNA microarray (see figure 1 and page 3631, column 1, where a Southern blot is a type of DNA microarray) which comprises sequences that detect intergenic regions, under conditions in which nucleic acid hybridization occurs (see figure 1 and figure 2, where hybridization clearly occurs throughout the region including in locations that are between genes as shown by figure 2, such as in the iab5 region),*

*h) comparing results obtained from said first label to results obtained from said second sample to identify the sequences of g) to which the DNA fragment hybridizes, whereby the region identified in h) is the region of the genome in the cell to which the protein of interest binds (see figure 1, figure 2 and page 3622, column 2, where Strutt*

teaches a comparison of the control to the sample to identify the region in which the proteins of interest bind).

With regard to claims 1, Strutt teaches hybridization to a southern blot, which is a type of microarray as discussed above (see figure 1).

With regard to claims 2 Strutt teaches the use of *Drosophila melanogaster* cells which are eukaryotic (see page 3630, column 1).

With regard to claims 3, Strutt teaches the use of DNA binding transcription factors (see page 3621, columns 1 and 2).

With regard to claims 4, Strutt teaches crosslinking with formaldehyde (see page 3630, column 2).

With regard to claims 5, Strutt teaches the use of antibodies to bind the protein of interest (see page 3630, column 2).

With regard to claims 6, 90 and 91, Strutt teaches the use of a ligation mediated PCR since the linkers must be ligated prior to PCR (see page 3631, column 1).

With regard to claims 8, Strutt teaches the use of a control (see 3623, figure 1).

With regard to claims 17, Strutt teaches shearing the DNA to make fragments (see page 3622, column 1).

With regard to claims 87, Strutt teaches identifying a DNA binding site of the protein where the protein is a transcription factor (see figure 4).

With regard to claim 88, Strutt teaches sequences that are located over a region of the *Drosophila* chromosome (see figure 2).

Strutt does not teach an additional step of blunting DNA fragments performed after the sonication step (although it is inherent in Strutt that at least some blunt-end fragments are produced during said sonication step; otherwise, the Strutt method would not have worked). Also, Strutt does not teach the use of two colors of fluorescent labels to compare the control and test samples in the place of the radioactive samples and Strutt does not teach a traditional "microarray", teaching only the use of Southern blots.

Page et al. disclose a blunting step following sonication of genomic DNA to obtain DNA fragments, followed by ligation of blunt end fragments to a blunt end PCR adapter (see column 11, lines 21-30).

Guilfoyle et al. disclose a "common procedure" for generating random overlapping DNA fragments which involves sonicating DNA and "polishing" (i.e., blunting) the ends of the resulting fragments by filling in with DNA polymerase "to help ensure that the majority of fragments are blunt-ended for higher efficiency of cloning" (see column 4, lines 37-43).

Schena teaches the use of two colors of fluorescent labels to multiplex samples on microarrays (see page 301 to page 302).

With regard to claims 15 and 16, Schena expressly teaches fluorescent labeling, showing a Cy5 fluorescently labeled microarray in figure 3.

Schena teaches the use of microarrays to analyze genomic information (see abstract).

One of ordinary skill in the art would have been motivated to modify the method of Strutt by adding a step of blunting DNA fragments following sonication, and before ligating to blunt-end adaptors, because as taught by either Page et al. or Guilfoyle et al. this would have expectedly provided for optimal ligation efficiency. That is, from the fact that the method of Strutt works without an additional blunting step prior to ligation to adaptors, it can be concluded that sonication of DNA yields a population of fragments, at least some of which have blunt ends. The fact that both Page et al. and Guilfoyle et al. do disclose such a separate blunting step indicates that said step would have been understood by the skilled artisan to be desirable and advantageous for the purpose of optimizing ligation, as the results of the blunting step would be to convert more of the population of sonicated fragments to blunt ends, which is necessary for ligation to take place to the blunt-end adaptors.

Further, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the fluorescent labels of Schena for the radioactive labels of Strutt since Schena expressly indicates that fluorescent labeling is



advantageous since "Novel labelling and detection methods, such those involving multicolour fluorescence, allow comparisons of multiple samples to be made on a single chip. Multiplexing increases the accuracy of comparative analysis by eliminating complicating factors such as chip-to-chip variation, discrepancies in reaction conditions and other shortcomings inherent in comparing separate experiments (see page 301-302)." This same logic would apply to the method of Strutt, since while Strutt does perform the hybridization to the same support, the hybridization does not occur at the same time under precisely the same reaction conditions, and an ordinary practitioner would recognize, from the motivation of Schena, that the use of two fluorescent labels would permit multiplexing the analysis under precisely the same conditions, eliminating many of the complicating factors in the analysis. Further, an ordinary practitioner would have been motivated to perform the substitution of the microarrays of Schena for the Southern blot of Strutt since Schena expressly notes "Although reminiscent of filter based assays, chip assays are a fundamental departure from techniques that employ porous membranes. Chips allow true parallelism, miniaturization, multiplexing and automation, and these key features provide a set of performance specifications that cannot be achieved with the earlier technologies (see page 301, column 2)." Schena is expressly teaching that chip assays are superior to the prior art filter based assays such as Southern blots of Orlando. Schena provides significant additional motivation to use microarrays in the place of such filter based assays noting,

"Microarray assays allow massive parallel data acquisition and analysis. Parallelism greatly increases the speed of experimental progress and allows meaningful comparisons to be made between

the genes or gene products represented in the microarray. Microarray assays may eventually allow the analysis of the entire human genome in a single reaction, and recent gene-expression experiments in yeast represent an important step towards this goal. Miniaturization of conventional assays is a general trend in biomedical research. Microscale assays reduce reagent consumption, minimize reaction volumes, increase the sample concentration and accelerate the reaction kinetics. Chip-based assays allow sensitive and rapid data detection with either confocal scanners or cameras equipped with charged-coupled devices. Although current microarray assays focus on nucleic acid hybridization, future studies will undoubtedly involve the parallel analysis of proteins, lipids, carbohydrates and small molecules. Multiplexing, the process by which multiple samples are analysed in a single assay, is another enabling feature of the microarray approach. Novel labelling and detection methods, such those involving multicolour fluorescence, allow comparisons of multiple samples to be made on a single chip. Multiplexing increases the accuracy of comparative analysis by eliminating complicating factors such as chip-to-chip variation, discrepancies in reaction conditions and other shortcomings inherent in comparing separate experiments (see page 301-302)."

An ordinary practitioner, motivated by Strutt to analyze genomic nucleic acids in order to identify regions of protein binding, would have been motivated by Schena to substitute the use of a microarray for the southern blot since Schena teaches that microarrays are faster, provide more meaningful comparisons, reduce reagent consumption and accelerate reaction kinetics, as well as increasing accuracy as discussed by Schena above.

Further, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the method of Strutt to the entire genome, as required by claims 88 and 92, in order to analyze the location of transcription factors

on the entire genome simultaneously. This is particularly obvious in light of Schena, who teaches analysis of genomic samples.

The ordinary practitioner is highly skilled in this art, at least a Ph.D. with years of experience as evidenced by the authors of the prior art. Dr. Schena is world renowned with a Ph.D. and 20 years of experience, Dr. Helen Strutt was a Ph.D. with years of postdoctoral experience. Dr. Giacomo Cavalli was a Ph.D. with years of postdoctoral experience. Dr. Renato Paro is a Ph.D. with more than 20 years experience who was a professor of molecular biology. Given this high level of skill, the use of a two color control on a microarray would have been prima facie obvious to these ordinary practitioners at the time of the invention.

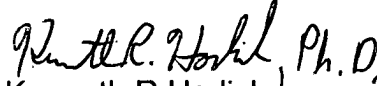
4. The arguments of the brief filed on 10/31/07 have been fully considered but are not found persuasive. The brief argues that Strutt does not teach an additional step of blunting DNA fragments performed after the sonication step, but this step is taught by each of the newly provided Page et al. and Guilfoyle et al. references. While the brief also argues that the claimed invention provides unexpected results, this is not found persuasive for the reasons already of record.

5. No claims are free of the prior art.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kenneth R. Horlick whose telephone number is 571-272-0784. The examiner can normally be reached on Monday-Thursday 6:30AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

  
Kenneth R Horlick, Ph.D.  
Primary Examiner  
Art Unit 1637

01/09/08